SUMMARY

Uncovering Physiologic Mechanisms of Circadian Rhythms and Sleep/Wake Regulation through Mathematical Modeling

Richard E. Kronauer,[*,†] Glenn Gunzelmann,[‡] Hans P. A. Van Dongen,[§] Francis J. Doyle III,[‖] and Elizabeth B. Klerman[*,1]

[*]*Division of Sleep Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA;*
[†]*Division of Applied Sciences, Harvard University, Cambridge, MA;*
[‡]*Air Force Research Laboratory, Mesa, AZ;*
[§]*Sleep and Performance Research Center, Washington State University, Spokane, WA;*
[‖]*Department of Chemical Engineering, University of California, Santa Barbara, Santa Barbara, CA*

Abstract Mathematical models of neurobehavioral function are useful both for understanding the underlying physiology and for predicting the effects of rest-activity-work schedules and interventions on neurobehavioral function. In a symposium titled "Modeling Human Neurobehavioral Performance I: Uncovering Physiologic Mechanisms" at the 2006 Society for Industrial and Applied Mathematics/Society for Mathematical Biology (SIAM/SMB) Conference on the Life Sciences, different approaches to modeling the physiology of human circadian rhythms, sleep, and neurobehavioral performance and their usefulness in understanding the underlying physiology were examined. The topics included key elements of the physiology that should be included in mathematical models, a computational model developed within a cognitive architecture that has begun to include the effects of extended wake on information-processing mechanisms that influence neurobehavioral function, how to deal with interindividual differences in the prediction of neurobehavioral function, the applications of systems biology and control theory to the study of circadian rhythms, and comparisons of these methods in approaching the overarching questions of the underlying physiology and mathematical models of circadian rhythms and neurobehavioral function. A unifying theme was that it is important to have strong collaborative ties between experimental investigators and mathematical modelers, both for the design and conduct of experiments and for continued development of the models.

Key words mathematical modeling, circadian, sleep, neurobehavioral performance, cognitive architecture, systems biology

Mathematical models of circadian rhythms and neurobehavioral function are useful both for understanding the underlying physiology and for predicting the effects of interventions and schedules on circadian rhythms and neurobehavioral function. In a symposium titled "Modeling Human Neurobehavioral Performance I: Uncovering Physiologic Mechanisms" at the 2006 Society for Industrial and Applied

1. To whom all correspondence should be addressed: Elizabeth B. Klerman, MD, PhD, Division of Sleep Medicine, Brigham and Women's Hospital, 221 Longwood Avenue, Boston MA 02115; e-mail: ebklerman@hms.harvard.edu.

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Mathematics/Society for Mathematical Biology (SIAM/SMB) Conference on the Life Sciences, different aspects of modeling of the physiology of human circadian rhythms, sleep, and neurobehavioral performance were examined. A common feature of all presentations was the importance of interactions between experiments and mathematical modeling. Experimental results provided data for initial conception and later development and validation of all the models. In turn, the mathematical models were used to clarify areas that required further experimentation. The results of these new experiments were then incorporated into the models.

The rationale for the workshop was that human neurobehavioral performance is influenced by circadian rhythmicity (from the endogenous ~24-h pacemaker), sleep-wake homeostasis (related to length of time awake or asleep), and sleep inertia (transient sleepiness upon awakening). Nonlinear mathematical models of circadian rhythms and performance test hypotheses regarding these underlying mechanisms and make predictions. This symposium showcased several mathematical approaches developed to understand and predict circadian rhythms, sleep, and neurobehavioral performance, including quantification of interindividual differences, computational modeling using a cognitive architecture, and the merits of a dynamic system that is robust yet stable. Also discussed by the presenters and audience participants were the data, experiments, and analytic tools required to create, test, and use these approaches.

KRONAUER: "RECENT PHYSIOLOGICAL DEVELOPMENTS"

Recent physiological developments have provided information that can be added to mathematical models of circadian rhythms, sleep, and neurobehavioral performance. In some cases, mathematical models provided the impetus for the experiments that detailed these results. In turn, these results should be incorporated into the next versions of appropriate models.

The first recent physiological development is identification of the photopigments and associated physiological responses that convey photic information to the central mammalian circadian pacemaker located in the SCN of the hypothalamus. The neural pathway from the retina to the SCN has been identified as the axons of a special set of large-soma, large-dendritic-field, ganglion cells (less than 0.2% of all retinal ganglion cells) that are also intrinsically photosensitive—hence their designation "ipRGC." The intrinsic photopigment is melanopsin, which has the standard spectral sensitivity of a Dartnall nomogram peaking at approximately 480 nm. These ganglion cells' dendrites also convey signals synaptically from rods and cones located over the entire human retina. In vitro spike recordings show vigorous response to both rod and cone stimulation (Dacey et al., 2005). Thus, the SCN probably receives information from ipRGC, rods, *and* cones, although the relative contributions and interactions of these sources remain to be identified.

A second development is possible identification of the neural populations involved in sleep and wake homeostasis. The descriptive "Process S" proposed by Borbély (1982), in which S was considered to be a sleep substance that increases during wake and declines during sleep, now assumes a new embodiment. Borbély suggested that the transitions (sleep onset or wake onset) might be considered the action of threshold processes. The new view is linked to the identification of sleep-active neurons in the ventrolateral preoptic area (VLPO) (Gaus et al., 2002) that complement the monoaminergic wake-active neurons in the brainstem. Sleep-active and wake-active neural populations are mutually inhibitory. The neuromodulator adenosine accumulates during wake and, when strong enough, is presumed to release VLPO neurons from inhibition; their resulting activity inhibits wake-active neurons. The process is purportedly reversed as adenosine declines during sleep. Adenosine, or another physiologic compound (Fuller et al., 2006), would then have the characteristics to be the physiologic basis of Process S. The mutually inhibitory neuronal populations, together with the surrogate Process S, have the potential to serve as an autonomous 3-variable flip-flop switch that can be entrained by signals from the circadian SCN pacemaker.

A third development arises from experiments seeking to separate circadian and homeostatic influences on multiple physiological functions. It is expected that neurobehavioral function (NBF), whether objective (e.g., performance on different tests) or subjective (e.g., mood, subjective alertness), will depend both on the time awake since fully restorative sleep, t_a, and the phase of the circadian pacemaker, ϕ. A forced desynchrony protocol is unique in its ability to study NBF as a function of both t_a and ϕ (Czeisler et al., 1999). Briefly, by imposing a cyclic pattern of bed rest and wake time at a period, T, sufficiently removed from a subject's intrinsic pacemaker period, τ, the pacemaker

will disentrain or desynchronize and run at its intrinsic τ. Under these conditions, sleep and wake will be sampled at all circadian phases. For any selected t_a, the dependence of NBF on ϕ can be subjected to Fourier decomposition. All Fourier coefficients thereby become functions of t_a. The Fourier constant (the average over ϕ), because of its independence from ϕ, is designated the "homeostatic component" $H(t_a)$ for any selected NBF. Of the various periodic Fourier components, so far only the fundamental has been reliably distinguished above data "noise" for NBF (Jewett and Kronauer, 1999), so the circadian influence on the NBF is represented as

$$C(t_a) = A(t_a) \cos (\Theta(t_a)+\Psi_i). \quad (1)$$

Some measures may require higher harmonics (e.g., ~12 h, ~8 h, or more frequent) to represent NBF or other physiologic variables. Brown and Czeisler (1992) found that a 2-harmonic representation for core body temperature was all that could be reliably extracted above noise in a constant routine protocol. The daily circadian pulse of plasma melatonin has been fit with 3 harmonics.

Some general properties appear to apply to both objective and subjective NBF in this decomposition. The homeostatic component, $H(t_a)$, declines with time awake—slowly at first, then more rapidly with a maximum rate of decline achieved after about 20 waking hours. The circadian component amplitude, $A(t_a)$, is extremely small at wakeup and rises exponentially to saturation with a time constant of about 11 h. The reference phase for the circadian component, $\phi_a(t_a)$, is approximately independent of t_a and is such as to produce the maximum of circadian-based performance approximately 13.5 h after the minimum of endogenous core body temperature, or approximately 7 PM in individuals with normally entrained circadian phase. The current Kronauer-Jewett model (Jewett and Kronauer, 1999) includes linear and nonlinear combinations of circadian (C), homeostatic (H), and linear contribution of sleep inertia processes. The increase of the circadian contribution to NBF during the working day opposes the homeostatic decline, leading to a remarkably uniform level of performance for $t_a < 12$ h. For $t_a > 15$ h, there is a precipitous decline in NBF as the 2 processes combine their negative effects. This provides a simple understanding of a major contribution to the human error that was a significant component of various disasters occurring around 3 AM (e.g., Chernobyl, 3 Mile Island, Exxon *Valdez*).

It is well understood that sleep regenerates NBF. Studies on sleep restriction, when sleep occurs at conventional hours, show that recovery is largely accomplished during the first 4 h (Jewett, 1997). This corresponds approximately to the predominant time of slow-wave sleep that Borbély (1982) proposed as characterizing the recovery of Process S. It is well documented that sleep at "adverse" circadian phase (i.e., ordinary waking hours) is less efficient with more and longer wake bouts (Dijk and Czeisler, 1994). The progressive regeneration of H (as described above) during sleep at adverse phase has not been documented and is of considerable importance in devising countermeasures to sleep restriction or deprivation and in understanding the effect of napping.

A fourth area of investigation is the effect of workload (e.g., the number and duration of performance-measuring bouts scheduled during the waking day) on NBF: workload may cause *H* to degrade more rapidly. Evidence to support this concept is not well organized but strongly suggestive. This is another topic for which carefully planned studies could be very useful. Jewett (Jewett et al., 1999a; Jewett and Kronauer, 1999) proposed that the homeostat could be described as a process whose rate of change depended on the present value, allowing for the probable dependence of degradation rate on workload. This proposal can be simply expanded:

$$(dH/dt_a) = K(\text{load})\, F(H), \quad (2)$$

where *H* represents the value of the homeostatic parameter, as described above (Jewett and Kronauer, 1999). That is, the effect of workload can be modeled as a simple multiplication function. For those interested in modeling performance, data on the effect of workload will be important. Experimental evidence regarding the role of neurobehavioral workload as a possible mediator of the expression of alertness deficits is forthcoming (Stakofsky et al., 2005).

A fifth area of investigation is sleep restriction, in which subjects experience a decreased amount of sleep over multiple days. Sleep restriction may be contrasted with acute sleep deprivation in which subjects experience a single, continuous wake episode. Previous mathematical models were derived from acute sleep deprivation data. However, recent data suggest that the effect of chronic sleep restriction is different from that with acute sleep deprivation on multiple physiological measures. Dinges and Van Dongen (Van Dongen et al., 2003) devised an elegant experiment to follow the cumulative effect on NBF of sleep restriction for 14 days. To maintain a fixed circadian phase for

sleep, the sleep/wake cycle for the experiments was 24 h. Of note, restriction of sleep implies extension of wake, so it is not clear whether less sleep or more wake is responsible for observed NBF degradation (Van Dongen et al., 2003). Consistent with the Jewett finding that daily NBF recovery is largely completed in the first 4 h of sleep (Jewett et al., 1999a), it is likely that cumulative NBF degradation may be due to the extension of wake time (Van Dongen and Dinges, 2003). In a 7-day sleep restriction study resembling that described above, Johnson et al. (2004) made the important observation that for 3-h time-in-bed, the cumulative NBF degradation was not fully restored even after 3 successive days with 8-h time-in-bed. This led the authors to postulate the existence of a second homeostatic process with very long time constants for degradation and recovery. The possibility that NBF homeostasis operates on 2 or more time scales is intriguing and needs further study.

Sleep inertia is the last physiological measure to be discussed here. Sleep inertia is the name given to the impairment of NBF seen upon arousal from sleep. The effect can be significant depending on the state of H and C upon awakening (e.g., Dinges et al., 1985). For cognitive performance, the deficit is comparable to the decline in H found at t_a = 12 h (Jewett and Kronauer, 1999). For subjective alertness, the deficit is even stronger. The time constant for dissipation of sleep inertia is on the order of 50 min, and impairment may still be detectable at 3 h (Jewett et al., 1999c). There is some evidence that wakeup from sleep at adverse phase may have stronger sleep inertia (Dinges et al., 1985; Rodgers et al., 2006).

The experimental results in these 6 areas have stimulated new thinking about the underlying physiology. Therefore, the results should be used to modify, test, and improve the models of circadian rhythms, sleep, and neurobehavioral performance. The revised models can then be used to design new experiments.

GUNZELMANN: "INTEGRATING BIOMATHEMATICAL MODELS WITH A COGNITIVE ARCHITECTURE"

Biomathematical models are an effective way of characterizing the overall modulatory effect of the human arousal system on NBF. By themselves, however, standard biomathematical models do not provide a detailed account of the impact of these modulating variables on cognitive processes. That is, they do not address the consequences of changes in alertness in terms of particular information-processing mechanisms and how they lead to observable changes in human performance. To address this issue, a theory of the human information-processing architecture is needed, in which the influences of these neurobehavioral systems can be explored in detailed models of human cognition and behavior. Such theories of human cognition exist (e.g., Anderson et al., 2004; Just et al., 1999; Newell, 1990). These *cognitive architectures* make theoretical claims regarding the representations, processes, and control structures that are available to the cognitive system. In cognitive architectures, cognition is represented as a set of information-processing mechanisms that allow the system to process and transform information encoded from the environment to generate human-like behavior.

Cognitive architectures have been used to create detailed models that make quantitative predictions about human cognition and performance (e.g., Anderson and Lebiere, 1998; Kieras and Meyer, 1997; Newell, 1990). However, there have been only limited, small-scale efforts to model the effects of decreased alertness on cognition (e.g., Jones et al., 1998; Jongman, 1998). The focus of this research effort is to implement mechanisms to account for the deleterious effects of reduced alertness within the ACT-R (Adaptive Control of Thought–Rational) cognitive architecture (Anderson et al., 2004; Anderson and Lebiere, 1998), which embodies a general theory of human cognition. This theory includes an account of how declarative knowledge (i.e., facts and information) is acquired, learned, and forgotten over time, as well as a theory of how procedural knowledge (skills and actions) is represented and learned to use declarative knowledge in performing a variety of tasks in a number of domains of psychological research (for a review, see Anderson and Lebiere, 1998). In addition, ACT-R includes mechanisms for perception and motor action (Byrne, 2001; Byrne and Anderson, 1998) based on a vast psychophysical research literature. Recent efforts have resulted in a mapping of mechanisms in the architecture to particular areas on the brain, exposing how cognitive mechanisms may be instantiated in physiological processes (Anderson et al., 2004).

Despite its breadth of coverage, ACT-R does not contain a theory of human alertness/fatigue or of the changes in information processing that occur as a function of circadian rhythms and sleep homeostatic processes. One goal of our research is to integrate an account of these processes into ACT-R and to specify

how the human arousal system affects information-processing activities in other portions of the brain. Understanding these impacts will shed light on the physiological processes through which the human arousal system functions and why decreased arousal leads to impaired performance on a variety of tasks. To accomplish this, we are incorporating existing biomathematical models of alertness into ACT-R to represent the dynamics of that system and to serve as the basis for influencing cognitive processes in the architecture. By linking changes in alertness to changes in parameter values in ACT-R's information-processing mechanisms, predictions can be made regarding how cognition changes under conditions of fatigue. In addition, identifying the mechanisms in ACT-R that are affected by decreased arousal will lend insight into the physiological changes that occur in particular areas of the brain, as well as enhancing our understanding of the consequences of those changes in terms of cognitive functioning.

In our initial efforts, we have focused on the psychomotor vigilance task (PVT), a sustained attention task that is sensitive to the effects of sleep loss (Dinges and Powell, 1985). In this task, participants monitor a known location on a computer screen and respond as quickly as possible when a stimulus appears. The stimulus appears at a random interval from 2 to 10 sec, and a session lasts for 10 min. Increased wake duration results in more erratic performance, including a greater probability of both false starts (anticipations) and lapses (reaction times greater than 500 msec). We have developed a model, using ACT-R, that performs this task, including perceptual operations for encoding the stimulus from the computer screen and motor operations for generating a response. The model produces quantitative performance predictions for each individual trial for the task. Thus, the model can be exposed to the same experimental procedure as participants, and the model's performance can be compared directly to the human data.

To account for the effects of extended wakefulness on performance, we have identified mechanisms in the architecture that 1) are linked to the cognitive requirements of performing the PVT and 2) are associated with brain regions that have been shown to be affected by sleep loss (Gunzelmann et al., 2007). The mechanisms identified are associated with *central cognition* in ACT-R, which is implemented as a serial production system. Within this component of the architecture, mechanisms control the selection and execution of the next cognitive action (represented as condition-action production rules). Selecting a single production to fire in ACT-R from potentially many possible candidates involves computing an expected utility (U) for each matching production using the following equation:

$$U_i = P_i G - C_i + \varepsilon. \quad (3)$$

In this equation, P_i is the probability of successfully achieving the goal with the production, C_i is the anticipated cost of achieving the goal with the production, and G is an architectural parameter that we associate with alertness. Finally, noise (ε) is added, resulting in stochasticity in the selection process.

In the model, reduced alertness is represented by decreasing the value of G. This results in lower values for U for each of the productions (when $P_i > 0$), which makes it less likely that a given production will exceed the utility threshold, T_u. In the event that no production exceeds T_u in a given selection cycle, no action is executed during that cycle's execution period. This can be thought of as a "micro-lapse," where ACT-R's cognitive system is inactive for a brief time (approximately 50 msec). The addition of noise to the utility calculation makes it possible that no action will occur on one cycle, followed by a cycle where a production does match and rises above T_u. Of course, it is also possible that multiple micro-lapses will occur in succession, resulting in significant degradations in performance on the PVT. To capture the dynamic process of falling asleep, we assume that a micro-lapse is indicative of alertness decreasing during the course of an individual trial. Thus, when a micro-lapse occurs, G is decremented slightly, which increases the probability that micro-lapses will occur on subsequent cognitive cycles. G is restored to its initial value at the beginning of each trial since trials end either when participants respond or when they are alerted by an experimenter after failing to respond within 30 sec of the appearance of a stimulus.

Our account has emerged after consideration of several other existing possibilities of how fatigue affects cognition. We evaluated the impact of slower cognitive processing and increased noise, separately and in combination, on the performance of our ACT-R model. These alternative processes were unable to explain the complex pattern of results associated with the PVT. Other cognitive consequences of fatigue are also being tested, including its effect on learning. Our model for the PVT does not include the impact of fatigue on learning because there is no evidence of learning on that task. As the theory is expanded and a more comprehensive set of

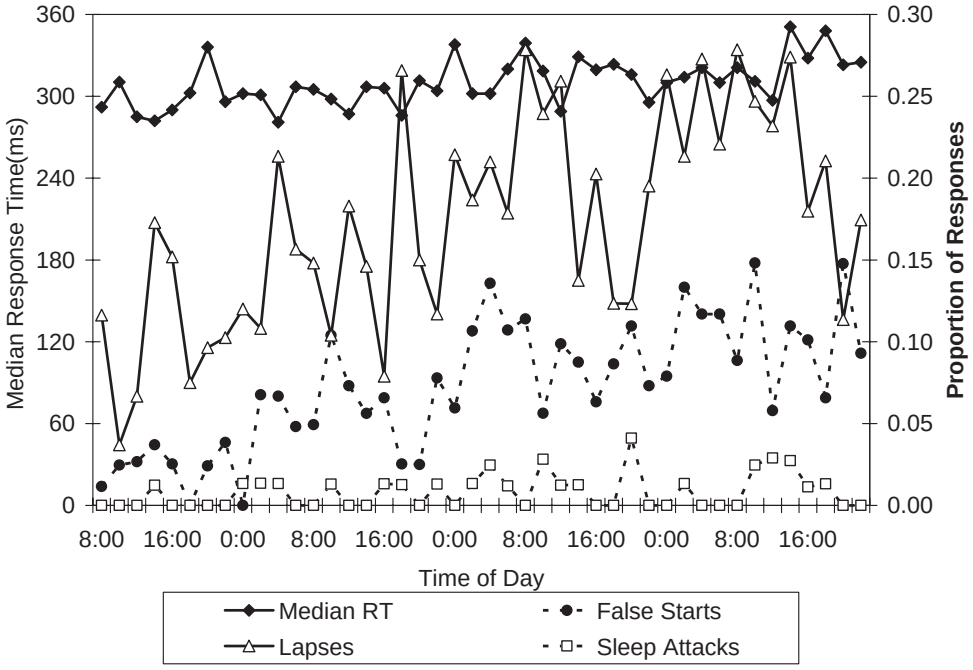

Figure 1. Performance of the integrated ACT-R (Adaptive Control of Thought–Rational)/biomathematical model across 88 h of total sleep deprivation. The data represent a single iteration of the model through the protocol, illustrating the variability in performance that is possible in the model while still capturing the effects of sleep loss and circadian rhythmicity emerging over the full length of the protocol.

mechanisms is developed, these effects can be specifically addressed.

In addition to identifying mechanisms within ACT-R that reflect the cognitive consequences of extended wakefulness, we have established an initial link between those mechanisms and the predictions of subjective alertness that are generated by 2 biomathematical models of sleep loss: the Kronauer-Jewett model (Jewett and Kronauer, 1999) and the Hursh Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) model (Hursh et al., 2004). In this integration, predictions of cognitive throughput (from the Kronauer-Jewett model) or effectiveness (from SAFTE) drive the changes that are made to the alertness (G)and utility threshold (T_u) parameters in ACT-R. G is decremented to represent decreases in alertness, whereas T_u is decremented to represent increasing attempts to compensate for the resulting impairments. These parameters have been mapped to alertness predictions. In this way, the dynamics of alertness in ACT-R are determined based on biomathematical models that incorporate what is currently known about circadian and homeostatic physiological influences in the arousal system. The links that have been proposed provide some suggestions regarding the impact that the outputs of the human arousal system may have on other physiological processes in the brain.

The integrated model is able to capture the dynamics of human performance on the PVT for multiple dependent variables across multiple days of sleep deprivation (Gross et al., 2006; Gunzelmann et al., 2005). Figure 1 presents the predictions from an individual run of the model for each of the 4 response types across 88 h of total sleep deprivation. There is significant variability in the model's performance on the task, but there is a clear trend toward worsening performance in the model as alertness decreases. Circadian rhythmicity is also apparent in the model, particularly with regard to the proportion of trials resulting in a lapse. While more iterations of the model produce lower variation and higher correlations to aggregate human data, the data in Figure 1 emphasize that the model participates in the experimental protocol just like an individual participant. It also illustrates the variability in performance that emerges from the interaction of mechanisms and parameter values in ACT-R. This level of detail in modeling human cognition and performance can serve to enhance and extend efforts at making predictions at the individual level, such as the approach described in the next section.

The integrated account of the impact of fatigue draws on the strengths of both biomathematical models and cognitive architectures. The biomathematical models can specify the details of the physiological changes that occur as the result of circadian rhythms or extended wake duration. The mechanisms in cognitive architectures, like ACT-R, specify the details of human information processing and how those

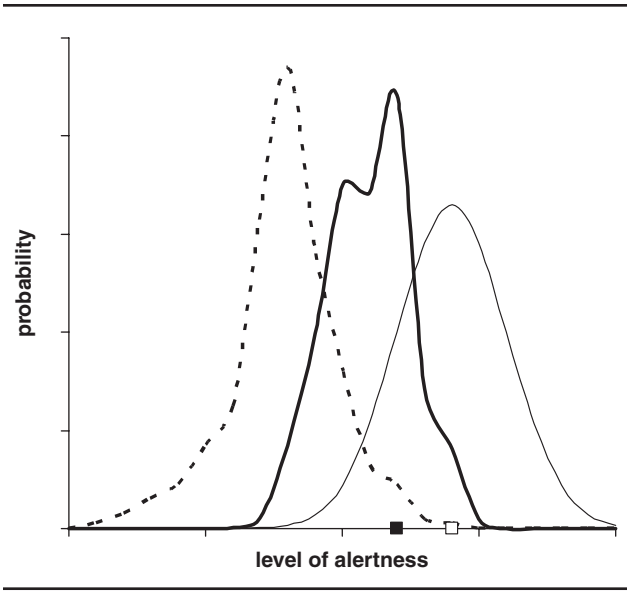

Figure 2. Conceptual representation of the Bayesian forecasting procedure. The approach considers both an individual's observed level of alertness (white box) with its statistical uncertainty (illustrated by the thin probability curve) and the likelihood of observing that level of alertness given the current model parameters and the population distribution of the model parameters (represented here by the dashed probability curve). Combining these probabilities (as reflected in the thick probability curve) serves to update the model parameters for the individual at hand and to generate subject-specific predictions for the true level of alertness in the present time (black box) and in the future (not shown).

mechanisms translate into observable human performance. In our research, these approaches have been combined, such that predictions about alertness or processing efficiency are used to drive parameter changes within the cognitive architecture to influence the functioning of the information-processing mechanisms. This provides a useful way to track the physiological impact of changes in arousal on other portions of the brain and to understand the changes in cognition that they represent.

VAN DONGEN: "MAKING ALERTNESS PREDICTIONS IN THE FACE OF SYSTEMATIC INDIVIDUAL DIFFERENCES"

Biomathematical models can be used to predict alertness deficits due to circadian rhythms and extended wake duration or sleep loss (Neri, 2004). However, there are considerable (Leproult et al., 2003), trait-like (Van Dongen et al., 2004a) individual differences in the alertness deficits resulting from sleep loss that are assumed to reflect differences in physiology among individuals. To be useful and reliable in operational settings, biomathematical models have to deal with these individual differences (Dinges and Achermann, 1999; Friedl et al., 2004). Yet, none of the currently available models can readily handle individual differences (Van Dongen, 2004).

A statistical technique called Bayesian forecasting offers a solution to this problem (Olofsen et al., 2004). The technique relies on advance characterization of the interindividual variability in alertness responses to sleep loss by studying a sample drawn from the population of interest. The sample does not need to include the individual(s) for whom biomathematical model predictions are going to be made, and the conditions under which the sample is studied do not need to be the same, provided they remain within the scope of the biomathematical model. Mixed-effects regression is applied to the alertness data from the studied sample to estimate systematic between-subjects variability in the biomathematical model parameters (Olofsen et al., 2004; Van Dongen et al., 2004b). For a new individual not studied beforehand, any observed level of alertness can be compared to the population variability in the model parameters, so as to find the specific parameter values that would best describe the new individual (see Figure 2). In this manner, only a handful of alertness measurements are needed from the new individual to obtain good estimates of this person's model parameters. Thus, the Bayesian forecasting technique allows for efficient optimization of a biomathematical model for the purpose of making subject-specific alertness predictions (Olofsen et al., 2004).

Here it is shown how this approach can be applied in the context of the 2-process model of sleep regulation (Borbély and Achermann, 1999). This model includes the above-mentioned homeostatic Process S, as well as a circadian Process C. Although not featuring the dynamic properties of contemporary models of the circadian pacemaker (Jewett et al., 1999b), the standard 2-process model has been used successfully to predict alertness in scenarios involving acute sleep deprivation (Achermann and Borbély, 1994). For a given individual *i*, the 2-process model equations for predicted alertness during wakefulness can be written as follows:

$$S_i(t) = \zeta_i\,(1 - \exp\{-\rho_i\,[t - t_0]\}), \tag{4}$$

$$C_i(t) = \gamma_i\,\Sigma_k\,a_k\,\sin(2\,k\,\pi\,[t - \phi_i]/\tau), \tag{5}$$

$$A_i(t) = C_i(t) - S_i(t) + \beta_i, \tag{6}$$

where S represents Process S ($S > 0$), C represents Process C, and A is predicted alertness; t denotes time, t_0 is the time of awakening, τ is the (fixed)

circadian period, and a_k are a number of constants signifying circadian harmonics ($k = 1, \ldots, 5$).

Free parameters in this representation of the 2-process model are the homeostatic buildup rate ρ, the asymptote for the homeostatic process ζ, the circadian phase ϕ, the circadian amplitude γ, and the basal alertness level β. There is reason to believe that these parameters vary systematically among individuals (Aeschbach et al., 1996; Finelli et al., 2000; Kane and Engle, 2002; Kerkhof and Van Dongen, 1996; Van Dongen et al., 2004a). To account for this variability, so-called random effects are introduced (Van Dongen et al., 2004b) as follows:

$$\rho_i = \rho_0 + R_i, \tag{7}$$

$$\zeta_i = \zeta_0 + Z_i, \tag{8}$$

$$\phi_i = \phi_0 + F_i, \tag{9}$$

$$\gamma_i = \gamma_0 + G_i, \tag{10}$$

$$\beta_i = \beta_0 + B_i, \tag{11}$$

where R, Z, F, G, and B are normally distributed, respectively, with standard deviations r, z, f, g, and b.

Given alertness data from a sample studied to characterize the interindividual differences in alertness responses to sleep loss, the free parameters can be estimated by means of likelihood estimation. The likelihood l_i of observing the data $Y_i(t_j)$ for subject i at time points t_j is given by

$$\begin{aligned} l_i(Y_i \mid \rho_0, \zeta_0, \phi_0, \gamma_0, \beta_0, R_i, Z_i, F_i, G_i, B_i, \sigma) \\ \propto \Pi_j\, p[Y_i(t_j) \mid A_i(t_j), \sigma], \end{aligned} \tag{12}$$

where p denotes a normal distribution, here with a mean of $A_i(t_j)$ and a standard deviation of σ (representing the error variance in the data). Integration over the assumed normal distributions for R_i, Z_i, F_i, G_i, and B_i yields the marginal likelihood L_i:

$$\begin{aligned} L_i(Y_i \mid \rho_0, \zeta_0, \phi_0, \gamma_0, \beta_0, r, z, f, g, b, \sigma) \\ = \int_{R_i}\int_{Z_i}\int_{F_i}\int_{G_i}\int_{B_i} l_i(Y_i)\cdot \\ p[R_i \mid 0, r]\, p[Z_i \mid 0, z]\, p[F_i \mid 0, f]\, p[G_i \mid 0, g]\, p[B_i \mid 0, b]\cdot \\ dR_i\, dZ_i\, dF_i\, dG_i\, dB_i, \end{aligned} \tag{13}$$

where each integral runs from $-\infty$ to ∞. The likelihood L of observing the entire data set, Y, for all subjects in the sample is given by

$$L(Y \mid \rho_0, \zeta_0, \phi_0, \gamma_0, \beta_0, r, z, f, g, b, \sigma) = \Pi_i\, L_i(Y_i). \tag{14}$$

By maximizing L, the parameters are found that best describe the sample and thereby characterize the variability in the 2-process model parameters as represented by standard deviations r, z, f, g, and b.

In the Bayesian forecasting technique, this information is used to optimize the model parameters for a new individual, indicated here with a subscript *, by maximizing the following standard Bayesian expression (Olofsen et al., 2004):

$$\begin{aligned} l_*(Y_* \mid \rho_0, \zeta_0, \phi_0, \gamma_0, \beta_0, R_*, Z_*, F_*, G_*, B_*, \sigma)\cdot \\ p[R_* \mid 0, r]\, p[Z_* \mid 0, z]\, p[F_* \mid 0, f]\, p[G_* \mid 0, g]\, p[B_* \mid 0, b], \end{aligned} \tag{15}$$

where Y_* are the subject's data. Initially, no data may be available for the individual, in which case the parameter estimates are those that would correspond to the average subject in the previously studied sample. As soon as 1 or more alertness measurements are available for the new subject, however, maximization of the Bayesian expression yields parameter estimates which converge to the values that best characterize the individual. Provided the 2-process model remains valid under the circumstances at hand (but regardless of whether the sleep loss is the same as during the study conducted in advance to characterize a sample from the population), this results in progressively more accurate predictions of the subject's alertness for times ahead.

Although space limitations preclude further illustrating this procedure, its effectiveness can be demonstrated both theoretically (Olofsen et al., 2004) and with computer simulations. The latter approach is employed in ongoing research, involving an expansion of the Bayesian forecasting technique needed when dropping the assumption made here that the 2-process model parameters ζ and ϕ are trait like (Van Dongen et al., personal communication, 2006). This generalization of the technique allows for making subject-specific alertness predictions even if a person's circadian phase position and/or initial homeostatic level may be shifted (e.g., after transmeridian travel). Such work constitutes further progress in rendering biomathematical models useful and reliable for the prediction of neurobehavioral deficits due to extended wakefulness or circadian phase in operational settings.

Trait individual differences provide a new dimension for the study of waking neurobehavioral function (Van Dongen et al., 2005). These differences likely have some representation in the sleep/wake physiology, and identifying the physiological correlates will help to characterize and understand the underlying neurobiology. Considering individual differences in biomathematical model parameters may contribute to achieving that goal.

DOYLE: "SYSTEMS APPROACHES TO UNDERSTANDING ROBUSTNESS AND PERFORMANCE IN CIRCADIAN RHYTHMS"

As progress occurs in mathematical modeling of circadian rhythms at the molecular, cellular, and whole animal level, issues related to robustness of the models and of the circadian system in general have arisen. Methods for approaching these issues have been developed in classic control and systems biology theory. One of the key goals of systems biology is creating an understanding of biologic network behavior and the underlying physiology through the application of modeling and simulation and tightly linked to experiments. Systems biology focuses on the physiologic "system," rather than isolated genes or cells within the system. An example of this approach is the recognition that the phenotype of an organism is probably linked to networks at the molecular or cellular level, rather than single gene expression. In such a paradigm, it is useful to think of biological control as layered and hierarchical. One goal is to pinpoint the areas of robustness ("insensitivity") and fragility ("sensitivity") within the biological networks. This approach is situated in the more general context of systems biology and the techniques used to identify core principles in biophysical networks.

The tools from classic sensitivity analysis were applied to unravel design principles in complex biophysical networks, particularly with regard to robustness. A recurring theme that has emerged over the past several years is that complex network architectures are *robust yet fragile* (Csete and Doyle, 2002; Stelling et al., 2004b). For circadian oscillators, this can be illustrated at both the gene regulation level and the cell level: the system is robust in response to some (mostly external) perturbations but fragile in response to some (mostly internal, e.g., gene or receptor mutation) variation. The relative robustness/fragility can be quantified. For example, to define sensitivity as a measure of the impact of a perturbation on the performance, the following linear (first-order) equation can be used where the sensitivity (S) at time t is a function of the change in y relative to the change in p:

$$S_{ij}(t) = (\partial y_i / \partial p_j)(t). \quad (16)$$

For example, the variable y may be the concentration of a protein or a transcript in the circadian circuit, and p may represent a rate constant in the model (e.g., degradation rate). The Fisher information matrix is used to compute the relative weights of these sensitivities and identify individual perturbations, p, to which the system is relatively sensitive or robust. Software for these calculations is available using the toolkit BioSens, which has been developed as part of the DARPA open-systems approach to developing a toolkit for systems biology (http://www.chemengr .ucsb.edu/~ceweb/faculty/doyle/biosens/BioSens.htm).

In gene regulation, there are trade-offs in global versus local function (Stelling et al., 2004a) for robustness in timekeeping. For example, the 2-loop architecture of the genetic pathways creating the ~24-h cycle period improves clock precision. At the cellular level, it is well known that circadian oscillations are robust against temperature perturbations, but recent evidence suggests that individual cells are dependent on signaling from other cells to maintain a stable period with minimal cycle-to-cycle variability (Aton et al., 2005), and hence they are fragile to "attack" via disabling the receptors for those peptides. The relative robustness/fragility of different components of the system will affect the response of the system to extrinsic stimuli. Ideally, the system should not have a uniform and sensitive response to all stimuli; robustness is an important feature for operating under uncertainties.

In the context of both *engineering* and *biological* systems, robustness analysis requires the specification of 1) a system to be analyzed, 2) performance attribute, and 3) characterization of robustness. Failing this, it is impossible to give a rigorous answer to the following question: is it robust? This precludes vague questions such as, "Is the cell robust?" and instead requires a more formal specification such as, "Is the cell's growth rate robustly controlled in the face of a particular disturbance (heat, pH, growth medium, etc.)?"

In the context of biological oscillators, this opens up the possibility of investigating robustness (i.e., design principles) for a variety of metrics, including amplitude of oscillations (e.g., in protein concentration), period of oscillation, and phase of oscillation. For phase of oscillation, there are multiple interpretations: phase can refer to the position relative to ZT (zeitgeber time), or it can refer to the relative phase between 2 components in the system (e.g., mRNA and corresponding protein in a particular phosphorylation state). For a mathematical model of the *Drosophila* circadian oscillator, the results for robustness varied widely across 8 different metrics for performance: (state) period, (phase) period, relative phase, state, shape, amplitude, corrected phase, and phase (Stelling et al., 2004a). Definitions of the various terms, as they

relate to circadian oscillations, can be found in Bagheri et al. (2005). The effect of stopping oscillations entirely has not yet been tested.

The common result for the various metrics is that *global* components that are part of the overall cellular machinery in the architecture tend to be fragile, while *local* (i.e., circadian-specific) elements tend to be robust (Stelling et al., 2004a). This points to a specific design principle for the feedback wiring in the circadian oscillator, with the biological circuit conferring precision in timekeeping in contrast to a traditional engineering feedback architecture.

Additional detail can be focused on the metric of phase. Phase is one of the more important attributes of the circadian clock, owing to the importance of synchronizing the clock to the endogenous phase of an entraining cue, such as light. New tools have been introduced for quantifying the dependence of phase response on the system parameters using isochron-based phase measures (Gunawan and Doyle, in press). The results from a *Drosophila* mathematical model can be compared for the role of period control rather than phase control of the system in achieving synchronization. There exist overlapping control mechanisms as well as specialized regulatory points for phase and period responses. Therefore, it is not surprising that it was shown that photic entrainment requires phase and period modulations in agreement with experiments. In particular, the mRNA transcriptions were found to preferentially regulate the phase response of the *Drosophila* circadian model. In addition, photic entrainment in this system, as defined by modulating the timeless (TIM) degradation, was identified to have comparable control over the phase and period responses, in agreement with literature evidence. Phase was found to be relatively fragile with respect to mRNA transcription and mRNA degradation and translation but relatively robust with respect to phosphorylation and nuclear transport. In contrast, period control was found to be relatively robust to changes in mRNA transcription and protein phosphorylation but fragile to degradation and translation and nuclear transport. The resulting classifications can be tested using genetic experiments to alter the kinetic of processes in the circadian gene regulation.

In addition, phase sensitivity can be used to *forward engineer* a solution to the problem of clock resetting. Using both phase response curves and "transient phase characteristics," a methodology exists to optimize the phase-resetting properties of the circadian clock. The sensitivity analyses reveal which components of the network can be used as optimal control variables since the system is "sensitive" and not "robust" to those measures with respect to changes in phase. Algorithms from the control engineering literature have been employed, notably model predictive control, to optimize the exposure of light in the resetting of a *Drosophila* model (Bagheri et al., 2005). The algorithm uses a model to predict the effect over several cycles of light and calculates the series of changes in 30-min intervals that minimize the time required to reset the phase. A range of initial phase mismatches was studied (i.e., varying degrees of jet lag), and the algorithm showed a rapid convergence rate—on the order of 3 to 4 days to reset phase offsets of up to 9 to 12 h.

This last result demonstrates the potential of robustness analysis at the gene regulation scale, for therapeutic solutions at the organism scale. To date, however, there are no molecular-scale mathematical models for human circadian rhythms, while the *Drosophila* and mouse models are generating insights. The connection to robustness analysis of human physiology remains an endeavor for continued research.

CONCLUSIONS

The ideas and results presented above include a variety of approaches to understanding the impact of sleep and circadian rhythms on human functioning. Despite the disparity in approaches, there is a common, shared goal of capturing the rich dynamics of neurophysiology and neurobehavioral functioning stemming from activity in the human arousal system. Our hope is that with ongoing research using multiple approaches, some convergence can be achieved.

There are many levels to span in this research. Detailed computational models of individual neurons and neuron populations, including the fragility and robustness of the interactions within and across populations, inform our understanding of physiological processes that give rise to circadian activity. Other models characterize alertness at a more abstract level, representing something like the cumulative output of entire neural structures and integrating the output of multiple components of the arousal system. The research developing cognitive models of human cognition and performance, in turn, uses those models in an effort to understand the implications of changes in alertness on cognitive processing. These models represent information-processing mechanisms spanning the entire brain to provide an account of the cognitive

processes involved in performing entire tasks. Finally, understanding individual differences in how alertness changes over time adds another dimension to this research by acknowledging that different people are affected differently by circadian rhythms and by sleep loss. Understanding those differences brings us closer to the goal of applying this research to improve overall performance and to prevent catastrophic breakdowns in human performance in applied settings and may also help us in understanding the physiological processes involved by exposing how they vary.

Given the diversity represented in this research, it may be challenging to bring these approaches together to generate a shared understanding of the physiology of the circadian pacemaker, sleep, and neurobehavioral performance. However, some avenues for achieving this goal are already emerging. The biomathematical models are informed by experimental and modeling work at the neuronal level. Better understanding of the detailed processes allows for more accurate conceptualizations of how to abstract from these to a more general account of arousal. Modeling the effects of decreased arousal in a cognitive architecture, in turn, is dependent on advancements made in biomathematical models of the arousal system since the outputs of the biomathematical models serve as the inputs to the cognitive architecture. Finally, understanding variability in human susceptibility to fatigue requires an account of the mechanisms involved and may suggest alternative accounts of the physiological mechanisms in the arousal system. In addition, techniques for identifying individual characteristics can also feed directly into cognitive modeling efforts to allow performance predictions to be made for particular people on specific tasks. This represents the ultimate applied goal for this area of research.

Each of these research areas presents unique and interesting research challenges to understanding the complex set of phenomena associated with this area of research. We are hopeful that success in individual areas of research can be integrated to provide a more comprehensive view of this component of human functioning. Recent advances illustrate the promise for achieving this goal. The continued interaction of individuals with experimental skills and resources with those with mathematical skills and resources will advance the field. The work described in this article describes progress that has been made along some fronts in this enterprise, and we look forward to extending these achievements with continued research effort.

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